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Helicobacter pylori Eradication in Patients on Long-term Treatment With NSAIDs Reduces the Severity of Gastritis

A Randomized Controlled Trial

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Background: Maintenance use of nonsteroidal anti-inflammatory drugs (NSAIDs) is often complicated by gastropathy. In non-NSAID users, eradication of *Helicobacter pylori* is associated with decreased mucosal inflammation, and may halt the progression to atrophy and intestinal metaplasia, but the continuous use of NSAIDs may interfere with these processes.

Goal: To investigate the effect of *H. pylori* eradication on gastric mucosal histology during long-term NSAID use, with and without gastroprotective therapy.

Study: Patients were eligible for inclusion if they were on long-term NSAIDs and were *H. pylori*-positive on serologic testing. Patients were randomly assigned to either eradication or placebo. Gastritis was assessed according to the updated Sydney classification for activity, chronic inflammation, gastric glandular atrophy, intestinal metaplasia, and *H. pylori* density.

Results: Biopsy specimens were available for histology of 305 patients. Of these, 48% were on chronic gastroprotective medication. Significant less active gastritis, inflammation, and *H. pylori* density was found in the eradication group compared with the placebo group in both corpus and antrum ($P < 0.001$). In the corpus, less atrophy was found in the eradication group compared with the placebo group.

Conclusions: *H. pylori* eradication in patients on long-term NSAID therapy leads to healing of gastritis despite ongoing NSAID therapy.

Key Words: nonsteroidal anti-inflammatory drugs, *Helicobacter pylori*, gastritis histology, proton pump inhibitor

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The authors confirm that there is no financial arrangement with the manufacturer of the drugs used in this study nor its competitor.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for rheumatic diseases. Maintenance use of NSAIDs is, however, often complicated by NSAID-gastropathy, which is characterized by dyspepsia, superficial mucosal damage, gastroduodenal ulcers, and even life-threatening ulcer complications.[1] Many strategies have been evaluated in recent years to prevent and treat gastroduodenal ulcers and their life threatening complications in NSAID users such as the addition of acid suppressive therapies, treatment with selective and specific cyclooxygenase-2 inhibitors, and eradication of *Helicobacter pylori*.[2–7]

H. pylori causes continuous gastric inflammation in nearly all infected persons.[8] This chronic inflammation persists throughout life and may lead to mucosal gland loss or atrophic gastritis, which may precede the development of intestinal metaplasia, dysplasia, and cancer.[9,10] Although NSAID use and *H. pylori* are the most common causes of peptic ulcers and their complications, and are frequently present in the same patients, the mechanisms of interaction require further study.[11]

Although many studies have shown that eradication of *H. pylori* causes resolution of active and chronic gastritis in non-NSAID users,[12–14] the effect of *H. pylori* eradication on gastric histology in patients on long-term NSAIDs is unclear because of a paucity of data.

One of the most effective and safest strategies to prevent ulcers is cotherapy with proton pump inhibitors (PPIs). However, profound acid suppressive therapy changes the extent of *H. pylori* gastritis into a corpus-predominant gastritis, which may accelerate the development of gastric gland loss.[15–17] The International Maastricht guideline therefore advises to consider *H. pylori* eradication in long-term PPI users.[18] This is of relevance for a considerable proportion of patients on long-term NSAIDs who are cotreated with acid suppressive therapy for many years. It is, however, unknown what the effect is of *H. pylori* eradication under these conditions.

Therefore we investigated, by means of a randomized, double blind, placebo-controlled study, whether *H. pylori* eradication changes gastric histology in patients receiving long-term treatment with NSAIDs, both in patients with and without gastroprotective cotreatment.

MATERIALS AND METHODS

Patients

Patients suffering from a rheumatic disease who were between 40 and 80 years of age were eligible for the study if

they were using NSAID on a long-term basis and were positive for *H. pylori* on serologic testing with enzyme-linked immunosorbent assay. Long-term NSAID treatment was defined as the use of any NSAID for at least 3 days a week during at least the previous month. Exclusion criteria were previous eradication therapy for *H. pylori*, allergy for the study medication (except amoxicillin) and presence of severe comorbidity. Concurrent use of steroids, low-dose aspirin, anticoagulants, and gastroprotective drugs were allowed. The presence of IgG-antibodies to *H. pylori* was determined with a commercial enzyme-linked immunosorbent assay Pyloriset new EIA-G (Orion Diagnostica, Espoo, Finland) according to the manufacturer's instructions. This assay has been assessed in the population under study and has proven a sensitivity and specificity in the Netherlands of 98% to 100% and 79% to 85%, even in patients on acid suppressive therapy.[19–21] The study protocol was approved by research and medical ethics committees of all participating centers and all patients gave written informed consent.

Study Design

After stratification by concurrent use of gastroprotective agents (PPIs, H_2 receptor antagonists, or misoprostol, but not prokinetics or antacids), patients were randomly assigned to receive either *H. pylori* eradication therapy with omeprazole 20 mg, amoxycillin 1000 mg, and clarithromycin 500 mg (OAC) twice daily for 7 days or placebo. Patients with an allergy for amoxycillin were randomized in a separate stratum to receive omeprazole 20 mg, metronidazol 500 mg, and clarithromycin 250 mg (OMC) or placebo therapy twice daily for 1 week. Randomization to consecutive patient numbers was done in proportions of 1:1, in blocks of 4 from a computer-generated list. The study centers were provided with individually sealed packages containing the treatment for each patient. Each center received entire blocks to be used sequentially. Rheumatologists were not practicing in more than one center. The study medication was given in a double blind, double dummy manner. Active and placebo preparations were identical in appearance. The employees of the VU University Medical Center pharmacy who packaged the medication only knew the assignment. It was disclosed to the treating physician only in case of emergency. All study personnel and participants were blinded to treatment assignment for the duration of the study.

Three months after study initiation patients underwent endoscopy of the upper gastrointestinal tract. Endoscopic findings were recorded systematically. The procedures were performed without sedation, or under conscious sedation using midazolam depending on patient's preference. The clinical results of the trial have been described elsewhere.[22]

Biopsies for histology and *H. pylori* culture were taken with standard biopsy forceps form the antrum ($\times 4$) and the corpus ($\times 4$). In the case of specific lesions additional samples were obtained but these were not part of this study.

Histology

All biopsies were routinely strained with hematoxylin-eosin. The slides were scored independently by an experienced gastrointestinal pathologist (E.B.) and the investigator (HdL), blinded to treatment assignment and clinical data, according to the updated Sydney classification.[23] Separate scores were given for *H. pylori* density, acute and chronic inflammatory component of gastritis, gastric glandular atrophy, and intestinal metaplasia. All items were scored from 0 (absent), to 1 (mild), 2 (moderate), or 3 (severe) as defined in the Sydney classification system. In case of discrepant results, the specimen was discussed until agreement was reached.

Statistical Analysis

The primary analysis was a comparison of treatment arms, irrespective of *H. pylori* status of individual patients. Measurements are expressed as mean and SD or as the median and interquartile range. Differences between groups were analyzed by χ^2 test and χ^2 test for linear trend (linear-by-linear association). Another analysis compared outcomes (the effect of *H. pylori* eradication) between stratum (the use of gastroprotective drugs or not) by computing the homogeneity of the common odds ratio. The level of significance was set at $P < 0.05$, 2 sided. SPSS software (version 11.0.0) was used to perform all analyses.

RESULTS

Patients

Three hundred forty-seven *H. pylori* seropositive patients were randomized in this study. A total of 172 received 1-week course of OAC whereas 175 received placebo. The treatment groups were similar in terms of demographic, rheumatic disease, drug use, and prognostic variables (Table 1). Our eligibility criteria resulted in a study group (61% women, mean age 59 ± 10 y) with mainly inflammatory rheumatic diseases, 48% of the patients used one or two gastroprotective agent (77% PPI, 14% H_2

TABLE 1. Baseline Characteristics of the 2 Groups (Eradication or Placebo)

Characteristic	Eradication (N = 172)	Placebo (N = 175)
Age—y*	59 ± 11	60 ± 10
Women	108 (63)	104 (60)
Underlying disease		
Rheumatoid arthritis	107 (62)	106 (61)
Spondylarthropathy	13 (8)	15 (9)
Psoriatic arthritis	14 (8)	11 (6)
Osteoarthritis	15 (9)	15 (9)
Other	23 (13)	28 (16)
Disease duration—y†	7 (3 to 14)	8 (3 to 15)
Gastroprotective treatment		
H_2 antagonist	9 (5)	14 (8)
PPI	64 (37)	63 (36)
Prostaglandin analogs (misoprostol)	0	1 (1)
NSAID treatment		
Conventional NSAID	118 (69)	116 (66)
COX-2 preferential NSAID (meloxicam, nabumetone)	27 (16)	33 (19)
COXIB (rofecoxib, celecoxib)	17 (10)	13 (7)
Combination drug (diclofenac/misoprostol)	10 (6)	13 (7)
Titer *H. pylori* serology†	1590 (692-3536)	1846 (799-4057)
Ethnic Dutch white	130 (87)	133 (87)
Known allergy for amoxycillin	10 (6)	12 (7)

*Plus-minus values are means ± SD; other values are counts (%) unless noted.

†Median (interquartile range).

receptor antagonists, 15% misoprostol) in combination with their NSAID therapy. No differences were noted between the treatment arms in terms of protocol violations.

Histology

In 20 patients in the eradication group and 22 in the placebo group gastric biopsies were not available for the following reasons: 16 patients withdrew consent for participation of the trial, 15 refused endoscopy, 7 used anticoagulants prohibiting biopsy sampling according the protocol, in 3 patients biopsy specimens could not be obtained because of discomfort requiring early completion of the procedure, and 1 patient died of cardiac arrest within 3 months after randomization. Histopathologic specimens could be assessed from 305 patients: 152 patients in the eradication group and 153 in the placebo group (Fig. 1).

Corpus

Corpus biopsy specimens were not available for 6 patients in the eradication group and 8 in the placebo group. Complete data from 291 subjects were available (as is shown in detail in Table 2 and Fig. 2). Corpus gastritis activity was moderate to severe in 4% of patients in the eradication group and in 35% of the placebo group ($P < 0.001$). Moderate to severe chronic inflammation was present in 28% in the corpus of patients in the eradication group. By comparison, moderate to severe chronic inflammation was observed in 65% of the placebo group ($P < 0.001$). Overall, moderate to severe corpus glandular atrophy was present in 10% of the eradication group and 22% of the placebo group ($P = 0.006$). Intestinal metaplasia of the corpus mucosa did not differ between groups and was present in 6% of patients. *H. pylori* colonization of the corpus mucosa was present in 11% of the eradication group and in 71% of the placebo group ($P < 0.001$).

Antrum

Antrum biopsy specimens were unavailable for 4 patients in the eradication group and 4 in the placebo group. Accordingly, data from 297 patients were available as shown in Table 3 and Figure 3. Antrum gastritis activity was moderate to severe in 3% of the patients in the eradication group and in 27% of the placebo group ($P < 0.001$). Moderate to severe chronic gastritis was present in 51% in patients in the eradication group in the antrum, and in 76% of the placebo group ($P < 0.001$). Antral glandular atrophy was scored moderate to severe in 33% in the eradication group and 41% in the placebo group (no significant difference). The presence of intestinal metaplasia did not differ between the groups in antrum and was present in 17% of all patients. *H. pylori* colonization of the antrum mucosa was present in 14% in the eradication group and 62% in the placebo group ($P < 0.001$).

TABLE 2. Histologic Characteristics of the Corpus, for Patients Randomly Assigned to Eradication Therapy or Placebo

Variable	Score	Eradication (N = 146)	Placebo (N = 145)	*P*
Activity	None	132	55	< 0.001
	Mild	9	39	
	Moderate	2	29	
	Severe	3	22	
Inflammation	None	7	3	< 0.001
	Mild	98	48	
	Moderate	30	60	
	Severe	11	34	
Atrophy	None	76	54	0.003
	Mild	55	59	
	Moderate	12	28	
	Severe	3	4	
Intestinal metaplasia	None	136	139	0.257
	Mild	6	4	
	Moderate	3	2	
	Severe	1	0	
H. pylori density	None	130	41	< 0.001
	Mild	6	28	
	Moderate	6	36	
	Severe	4	40	

Data are number of patients.

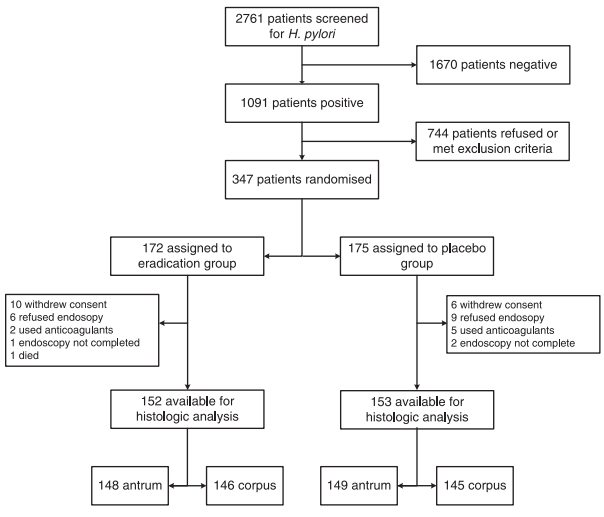

FIGURE 1. Trial profile and number of patients of whom specimens were available. Data are number of patients.

Analysis of the Effect of Eradication Stratified According to the use of Gastroprotective Drugs

Corpus

There were no differences between strata (according to the use of gastroprotective drugs) for the effect of eradication on active gastritis in the corpus ($P = 0.27$). A significant greater effect of eradication was found in patients on gastroprotective drugs for the presence of moderate to severe chronic inflammation in the corpus (22% and 74% in the eradication and placebo group, respectively) than in patients who did not take gastroprotective drugs (33% and 55% in the eradication and placebo group, respectively) ($P = 0.007$). No significant difference of effect of eradication was found in patients for the presence of corpus atrophy between patients using gastroprotection (42% and 68% in the eradication and placebo group, respectively) compared with in patients who did not take gastroprotective drugs (53% and 58% in the eradication and placebo group, respectively) ($P = 0.067$). There were no differences between strata for corpus intestinal metaplasia ($P = 0.10$). No difference was found

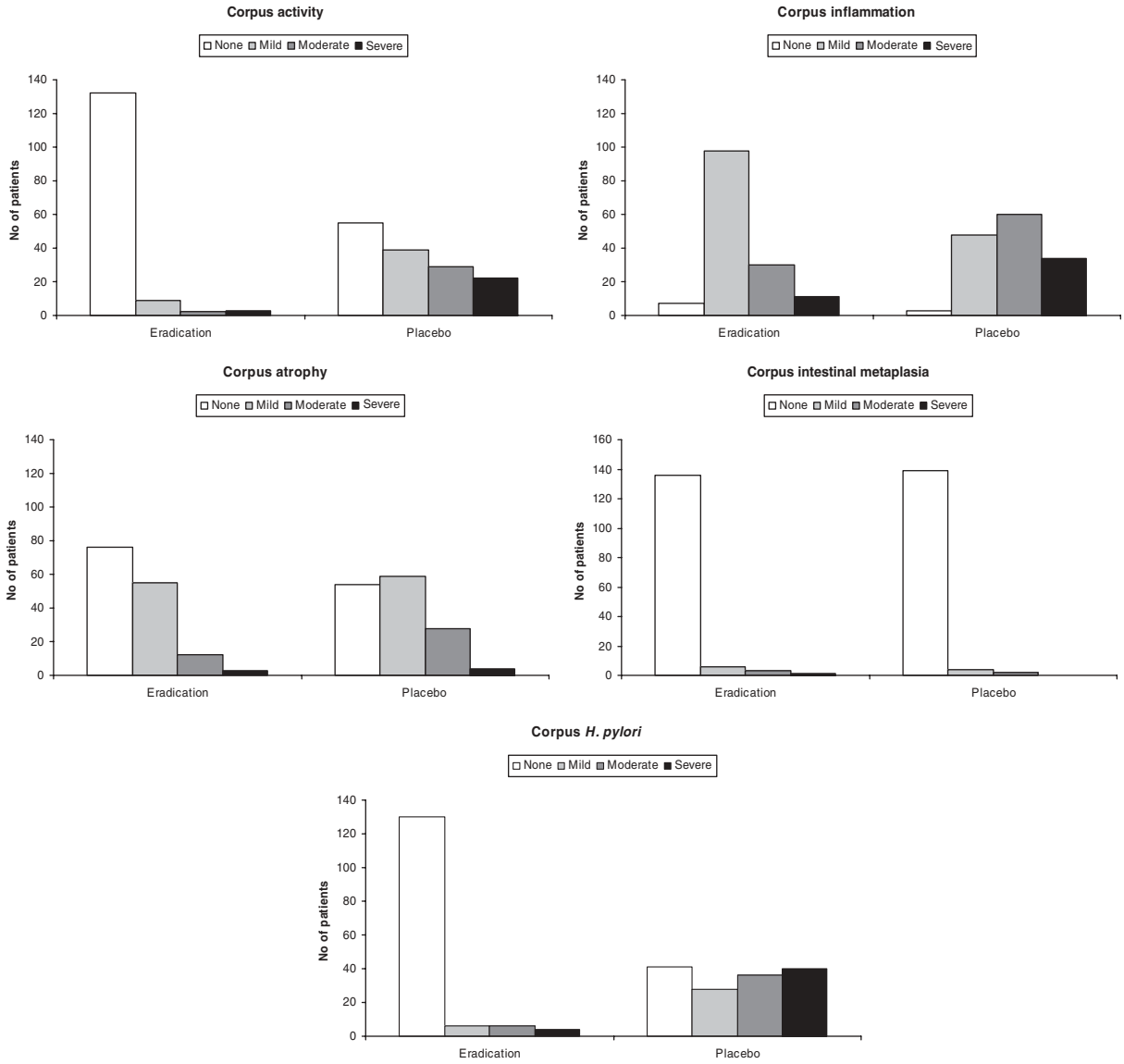

FIGURE 2. Gastritis scores for the corpus for eradication group and for the placebo group.

for effect of eradication therapy between strata on the presence of *H. pylori* ($P = 0.79$).

Antrum

In the antrum, the effect of eradication was not modified by gastroprotective drugs on active gastritis ($P = 0.81$), chronic inflammation in the antrum ($P = 0.99$), antrum atrophy ($P = 0.59$) nor antral intestinal metaplasia ($P = 0.052$). No difference was found for effect of eradication therapy between strata on the presence of *H. pylori* ($P = 0.29$).

DISCUSSION

The major finding of this large randomized, placebo-controlled study in long-term NSAID-users was that *H. pylori* eradication results in significantly lower acute and chronic gastritis scores despite ongoing NSAID use. An additional remarkable finding was that corpus atrophy scores were significantly lower in the *H. pylori* eradication group than in the placebo group.

Many studies have shown that eradication of *H. pylori* causes resolution of active and chronic gastritis in non-NSAID users.[12–14] Various studies addressed the potential interaction between *H. pylori* and NSAIDs on gastroduodenal mucosal damage. However, only few studies with limited number of patients regarded the effect of *H. pylori* eradication on gastric histology in patients on NSAIDs. In a small study of 11 *H. pylori* infected healthy subjects, high dose of naproxen for only 4 days had no effect on polymorphonuclear cells nor on *H. pylori* density.[24] A similar finding was reported in a study of 52 patients with rheumatoid arthritis who received NSAIDs for 1 month. No difference in severity of gastritis was found between

TABLE 3. Histologic Characteristics of the Antrum, for Patients Randomly Assigned to Eradication Therapy or Placebo

Variable	Score	Eradication (N = 148)	Placebo (N = 149)	*P*
Activity	None	126	66	< 0.001
	Mild	17	43	
	Moderate	4	27	
	Severe	1	13	
Inflammation	None	6	4	< 0.001
	Mild	66	32	
	Moderate	60	56	
	Severe	16	57	
Atrophy	None	9	4	0.181
	Mild	90	84	
	Moderate	42	56	
	Severe	7	5	
Intestinal metaplasia	None	124	124	0.890
	Mild	13	18	
	Moderate	8	5	
	Severe	3	3	
H. pylori	None	127	57	< 0.001
	Mild	9	22	
	Moderate	4	37	
	Severe	8	33	

Data are number of patients.

H. pylori-positive and *H. pylori*-negative patients.[25] In addition, in 118 patients receiving chronic NSAID treatment, the presence of *H. pylori* did not seem to increase histologic damage or ulcer prevalence.[26] In contrast, another study found that the presence of neutrophils increased the risk of ulceration in long-term NSAID users. Most of the inflammatory cells were found in *H. pylori*-positive patients. These patients had more severe gastritis and were thus at higher risk for ulcer disease.[27] Hence, these studies point out that there is no agreement on the effect of *H. pylori* on histologic characteristics in NSAID users. The present study with a high number of patients shows that eradication of *H. pylori* leads to significant reduction of active and chronic inflammation of both corpus and antrum mucosa within 3 months despite ongoing NSAID therapy. These findings support the proposition that *H. pylori* eradication might contribute to the prevention of NSAID gastropathy in chronic NSAID users. However, this seems not to be in line with data which are published elsewhere.[22] In that paper is described that *H. pylori* eradication therapy in patients on long-term NSAID treatment had no beneficial effect on the occurrence of ulcers, ulcer complication, erosions, dyspepsia, or quality of life. Nevertheless, the present study shows that *H. pylori* eradication improves the degree of gastritis in patients who are long term on NSAID treatment in the biopsy samples. Whether this effect has clinical consequences, such as the risk of development of ulcers or cancer on the long term has to be further investigated.

There is general agreement that acid suppressive therapy changes the usually antral predominant gastritis to one that is corpus predominant.[28,29] In addition, from studies of patients with gastro-esophageal reflux disease, there is growing evidence that *H. pylori* eradication in PPI users reduces mucosal inflammation and induces regression of corpus glandular atrophy.[15–17,30–32] These phenomena are relevant because the pattern of gastritis, with or without progression of gastric atrophy, is associated with an increased risk for the development of gastric cancer.[9] To assess the potential benefits of *H. pylori* eradication in this setting, most studies are designed to examine regression of precancerous changes, such as gland loss and intestinal metaplasia of the gastric mucosa as surrogate end points. A follow-up of many years would be necessary to confirm long-term clinical significance of *H. pylori* eradication for these premalignant parameters. Our data showed indeed, in both patients with and without treatment with gastroprotection, lower gastritis scores, and lower prevalence of atrophic gastritis of the corpus mucosa 3 months after *H. pylori* eradication and a significant greater effect of eradication on corpus inflammation in the gastroprotection group than in those who were not receiving gastroprotection. In the absence of baseline biopsy samples, it is not completely certain whether the difference is due to a regression of atrophic gastritis but the probability that the differences between groups was already present by chance at baseline is very small, as the randomized groups are large. A previous study showed a regression of atrophic gastritis after *H. pylori* eradication in patients with reflux esophagitis taking omeprazole maintenance therapy.[16] The first follow-up in the latter study, however, took place 12 months after eradication therapy. Probably, the same effect at an earlier stage is found in this study. As a large number of patients on long-term NSAIDs are treated with acid suppressive therapy for many years, eradication of *H. pylori* in these patients may be advisable to heal gastritis, in particular under the assumption that active gastritis increases the risk for NSAID gastropathy. Eradication may further prevent progression of atrophic gastritis, as its effect would be expected to persist.

Although the histopathology of *H. pylori* gastritis is associated with well-defined histologic features,[23] the spectrum and incidence of microscopic gastric lesions caused by chronic ingestion of NSAIDs is unspecific and still a matter of debate. Some investigators used Dixons' system for chemical gastritis but no correlation was found between the scoring system and endoscopic gastroduodenal damage.[26,33] Others concluded that there is no single histologic feature that can be used to characterize the diagnose chemical gastritis and simultaneous infection by *H. pylori* and thus makes the histologic diagnosis of chemical gastritis extremely difficult.[34] In this study, interpretation of the gastric biopsies was made as uniform and objective as possible by the use of predefined criteria of the updated Sydney System[23] and by blinded assessment of all biopsies by the same histopathologists.

We did not perform endoscopy at baseline, because invasive screening tests for *H. pylori* are less feasible in everyday practice. Instead, we used an assay for the presence of IgG-antibodies to *H. pylori*. This assay has been assessed in the population under study and has proven a sensitivity and specificity in the Netherlands of 98% to 100% and 79% to 85%, even in patients on acid suppressive therapy.[19–21] We analyzed the data according to treatment arm (intention to treat analysis). In practice one might retreat patients in case patients remain *H. pylori*-positive despite eradication therapy with antibiotics.

In conclusion, our study showed that *H. pylori* eradication in patients on long-term NSAID therapy leads to healing of gastritis despite ongoing NSAID therapy.

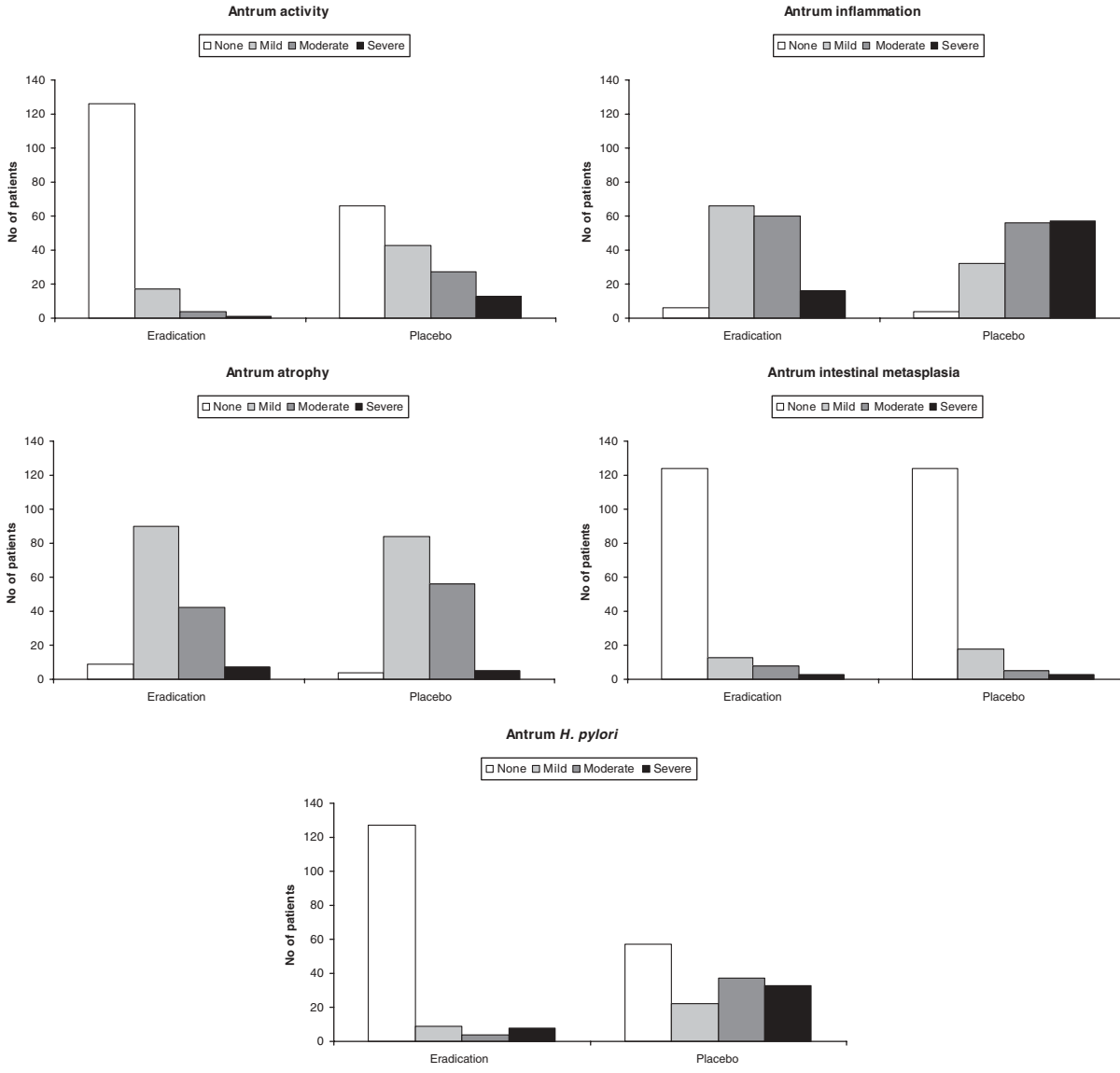

FIGURE 3. Gastritis scores for the antrum for eradication group and for the placebo group.

These data support the proposition that *H. pylori* eradication may reduce the severity of gastropathy in chronic NSAID users.

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